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Systematic Review and Meta-Analysis of Exercise Effects on Attention and Working Memory in Alzheimer's Disease

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SYSTEMATIC REVIEW AND META-ANALYSIS OF EXERCISE EFFECTS ON ATTENTION AND WORKING MEMORY IN ALZHEIMER'S DISEASE

by:
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ABSTRACT:

Studies have shown that exercise can have positive affects on cognition levels in patients suffering from Alzheimer's disease. A meta-analysis was conducted to see if exercise had an effect on attention or working memory in patients with Alzheimer's disease. A search was conducted through PubMed. From the initial search, 87 articles were found. Of these 87 articles, 2 met the criteria for analysis along with 1 additional article found from an additional source. These 3 articles were studied and a meta-analysis was performed. The Stroop Test was used to study attention scores and the Digit Span Test Backward test was used to study working memory scores. The analysis showed a decline in working memory with exercise. A slight improvement was seen in attention scores, but the results were statistically insignificant. The decline in WM might be more closely associated to the progression of the disease in participants, rather than the effect of exercise on working memory of patients. More studies should be conducted in order to further investigate these results.

TABLE OF CONTENTS:

LIST OF TABLES AND FIGURES:

LIST OF ABBREVIATIONS:

AD	Alzheimer's Disease
BDNF	Brain-derived Neurotrophic Factor
DSBW	Digit-Span Test Backwards
WM	Working Memory
MCI	Mild Cognitive Impairment
BW	Backwards

INTRODUCTION

Alzheimer's disease is a devastating neurological disease, which affects many people throughout the United States and the world. This disease induces a heavy burden on patients suffering from the disease, as well as their caregivers and families. It is a progressive disease that affects areas of the brain responsible for memory. The main areas of the brain affected in Alzheimer's patients are the hippocampus as well as other parts of the temporal lobe[15]. Mild Alzheimer's starts with memory loss associated with accumulation of beta-amyloid plaques outside neurons and tau protein deposits inside neurons in the brain[16]. The beta-amyloid plaques interrupt the ability of neurons to communicate to each other[16]. The tau proteins inside cells disrupt the electrical flow of signals in neurons and ultimately cause the death of cells[16]. As the disease progresses, memory loss becomes more severe and other symptoms develop as well including impaired reasoning and emotional instability[15].

In 2013 an estimated 5 million senior citizens, 65 years and older, were living with Alzheimer's disease in America[1]. With a growing overall population and an aging baby boomer population, the cases of Alzheimer's present in the United States are expected to increase dramatically[1]. According to one study the number of people with Alzheimer's could potentially rise to 14 million by the year 2050[1]. In 2010, the estimated cost of dementia in the United States was between $157 billion and $215 billion[2].

Medicare only covered $11 billion of this cost[2]. The number of Alzheimer's cases are expected to increase; therefore, the cost of the disease is expected to at least double or possibly more by 2040[2]. According to one study done by Brookmeyer and colleagues, if the onset of the disease could be delayed by 1 year, it might be possible to reduce the number of new cases by 9.2 million by the year 2050[4,9]. Alzheimer's is the most common neurodegenerative disease in the United States, and the sixth leading cause of death in the United States[17]. In recent years there have been many studies showing promising results in Alzheimer's patients who participate in physical activity programs.

There have been many studies testing the effect that exercise has on patients with cognitive impairments including mild cognitive impairment, Alzheimer's disease, and dementia. In some of these cases, exercise has been shown to increase cognitive abilities and have a positive effect on overall cognition[3, 4, 6, 17]. Exercise has been shown to have results such as decrease in heart disease, decrease incidence of cancer, decreased risk of diabetes mellitus, and decreased development of osteoporosis[3]. Studies have also shown that physical activity might delay cognitive impairments in patients at risk for cognitive loss[3]. If exercise is found to delay the effects of cognitive impairment, then it is possible that at risk patients could delay the onset of Alzheimer's and dementia with a participation in an exercise program. This would be a huge advance for not only people with Alzheimer's disease, but also people at risk for developing the disease.

There are several possible reasons why exercise might be potentially protective against cognitive loss. A meta-analysis of exercise on brain-derived neurotrophic factor (BDNF) showed an increase in this protein with participation in exercise programs[6]. This protein has been linked to neural functioning and development [6, 8]. The mechanism

for the potential effects of physical activity on cognitive function may be due to increase cerebral blood flow in the presence of physical activity[7]. Physical Activity may also increase cerebral nutrient supply and increase aerobic capacity[7]. Due to the positive effects of physical activity, it might be possible to increase cognitive abilities and decrease cognitive decline. Unfortunately, many senior citizens are generally less active than younger adults [19]. This could be due to a number of reasons some of which could include disability, no ability to access a workout facility, not learning how to be active, among many others. Even the senior citizens who are active and able to exercise are more than likely participating in lower intensity workouts compared to other younger adults[19]. While this is due mostly to the natural aging process, this is a significant disadvantage for senior citizens.

In order to test the validity of these results a meta-analysis was performed on published articles meeting the criteria for analysis. The results of these articles were studied. A systematic review and meta-analysis of these studies were conducted to determine if exercise had an effect on attention and working memory in Alzheimer's patients.

MATERIALS AND METHODS

In order to establish which studies were suitable for the meta-analysis, a PubMed search was conducted on December 15, 2014. The terms searched were [(((alzheimer[Title/Abstract]) OR dementia[Title/Abstract]) AND exercise) AND attention]. The first studies to be excluded were non-human studies. Following this, studies not including Alzheimer's patients were excluded. Next, articles not testing exercise were excluded. Then, articles not testing attention were eliminated. Following this step any review articles or articles without results were eliminated. One article was eliminated because it was a long-term epidemiological study. From the remaining articles, any article that included both a Stroop Test and a Digit Span test run backwards were selected for analysis. One additional article was found using an alternate resource. This process is shown in figure 1. Table 2 shows the title of each article that was found in the PubMed search, and the reason they were not chosen for the analysis.

RESULTS

The following results were obtained from the meta-analysis of the 3 articles meeting the specific criteria for the study. For the Stroop Test, meta-analysis did not show significant change in Stroop performance. It showed a slight improvement in attention scores, but the improvement was not significant. For the Digit span BW Test, meta-analysis actually showed a decline in Digit Span performance and working memory. The p value was equal to 0.0002, and the effect size was-0.80 with a 95% confidence interval of -1.22 to -0.37. Results from the working memory study are shown in figure 2. Results from the attention study are shown in figure 3. Some missing values from the studies were estimated.

DISCUSSION:

This meta-analysis was conducted using the metaphor R package[21]. The effects sizes for the studies were calculated using random effects model, in which effect size is found under the assumption that the samples were collected from non-homogeneous populations[20]. From the initial search, 87 articles were found. Of these 87 articles, 2 met the criteria for analysis along with 1 additional article found from additional source. These 3 articles were used the in meta-analysis. According to the results, exercise had adverse effects on working memory. Exercise showed a slight improvement in attention scores, but the results were statistically insignificant. According to the meta-analysis DSBW showed a decline in performance, reflecting a decline in working memory. In another meta-analysis, exercise was found to also have no significant effect on working memory[17]. Figure 3 shows the results from the DSBW and working memory. Of the studies included only 1 showed an increase in WM. Figure 4 shows the results of the Stroop Test and attention. Two of the 3 studies showed an increase in attention. However, these improvements were only slight. According to the results, exercise has no significant effect on attention, and exercise shows a decline in working memory.

The three studies included in the analysis all contained results from the Stroop Test and Digit Span Test Backward. The Stroop Test involves a series of color names written in either the color they represent, or a different color. The subject is supposed to

say the name of the color, without reading the word. For example, if the word green was written in the color red, the participate is suppose to say the word "red." This test is often difficult because the subject has to reject the automatic response to read the word, which can cause a delay in their response[5]. This delay is known as the "Stroop effect"[5]. This test was used to measure attention of patients in the studies used in the analysis [10, 11, 12]. When testing the working memory of the participates, the Digit Span Test Backwards was used. This test shows the participant a series of numbers. The subject must then repeat the numbers back, but in the reverse order in which they were shown the numbers[18]. For example, the participant would hear "1, 2, 3." The participant would then say back, "3, 2, 1." This test measures working memory in subjects. The three studies included in this analysis all used these tests in their experiments.

The articles examined in their paper were published between 2012 and 2014, which shows this data was relatively recent and still relevant. The study done by Arcoverde and colleagues lasted 16 weeks with 10 participants in the experimental group. It was published in 2013. The exercise, or experimental group, completed a walking program on the treadmill 30 minutes, 2 times a week. The study done by Bossers and colleagues was published in 2014. The studied lasted 6 weeks, and had 18 participants in the experimental group. The participants in the experimental group completed a walking and strength training session. They did 3 walking sessions a week and 2 strength training sessions a week. The final study done by Anderson-Hanley and colleagues was completed in 2012. The study was 90 days long and included 41 people in the experimental group. The exercise in this study included control bike.

The results indicated a decline in WM. This was suspected to be due to the

progression of the disease in participants, rather than the effect of exercise on the working memory of participants. One limitation of this analysis was the limited number of studies available meeting the criteria for analysis. If more studies were available, the results might have been altered. More studies need to be conducted in order to further investigate these results. An interesting area to further investigate would be to test if exercise has an effect on patients with MCI. These patients are at risk for developing Alzheimer's disease in the future[17]. Further studies might show exercise is more effective at preventing the disease, rather than reversing the effects of the disease.

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	Study	Year	Duration (days)	N	DigitSpanBW					Stroop					Exercise
					Before		After		MeanDiff		Before		After		MeanDiff		
					mean	SD	mean	SD			mean	SD	mean	SD			
A	Arcoverde et al.	2013	112	10	4.00	1.90			-0.90	1.50	2.20	1.40			0.81	1.60	Treadmill
B	Bossers et al.	2014	42	18	5.70	2.10	6.40	1.90	**0.70**	**2.00**	28.90	12.70	24.90	12.50	**-4.00**	**12.60**	Walking and Strength Training
C	Anderson-Hanley et al.	2012	90	41					-0.83	0.05					0.56	0.25	Control Bike

Table 1: Studies included in analysis

Note: Some values missing from the studies were estimated, which is shown in bold.

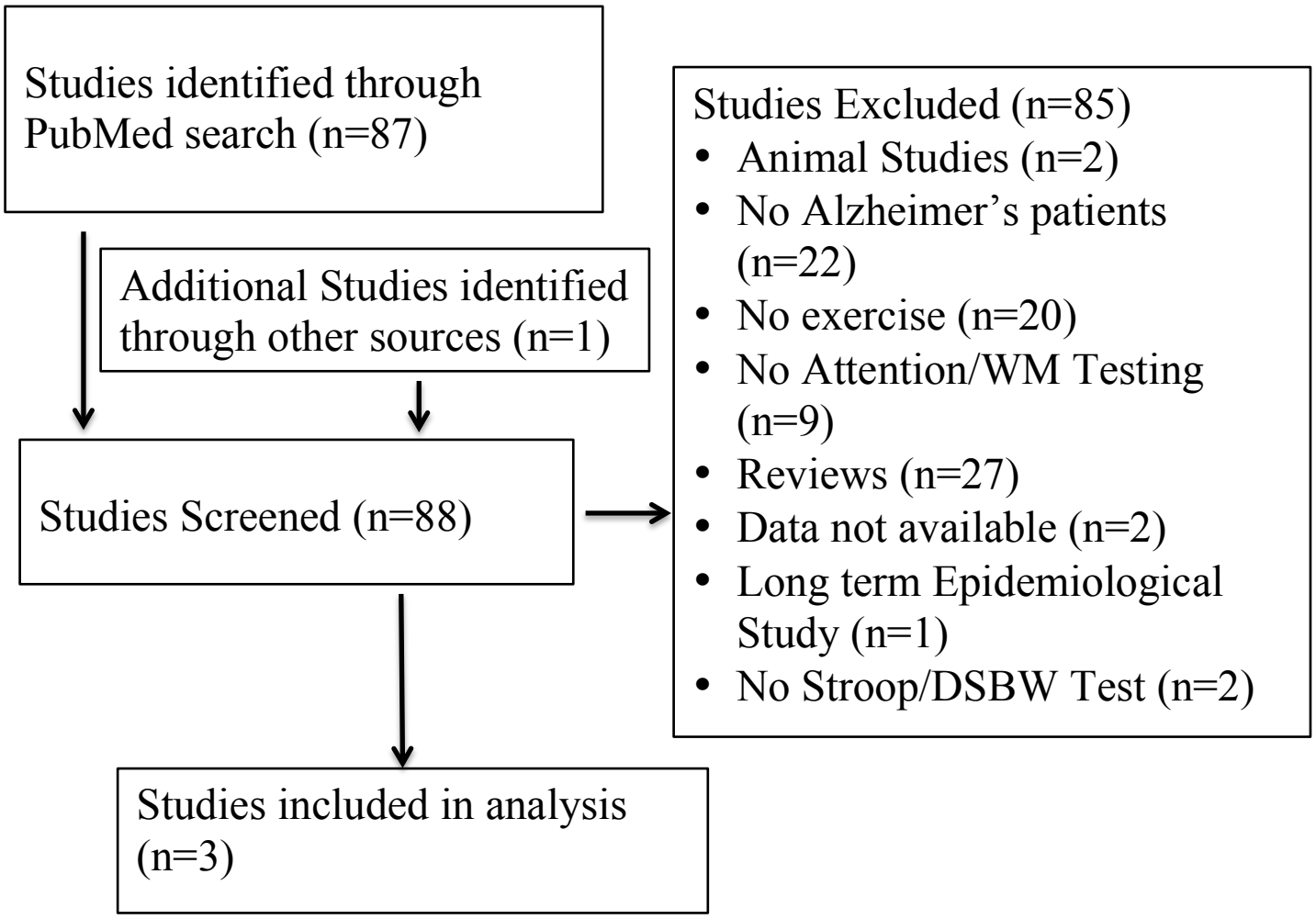

Figure 1: Flow diagram for identification of eligible studies

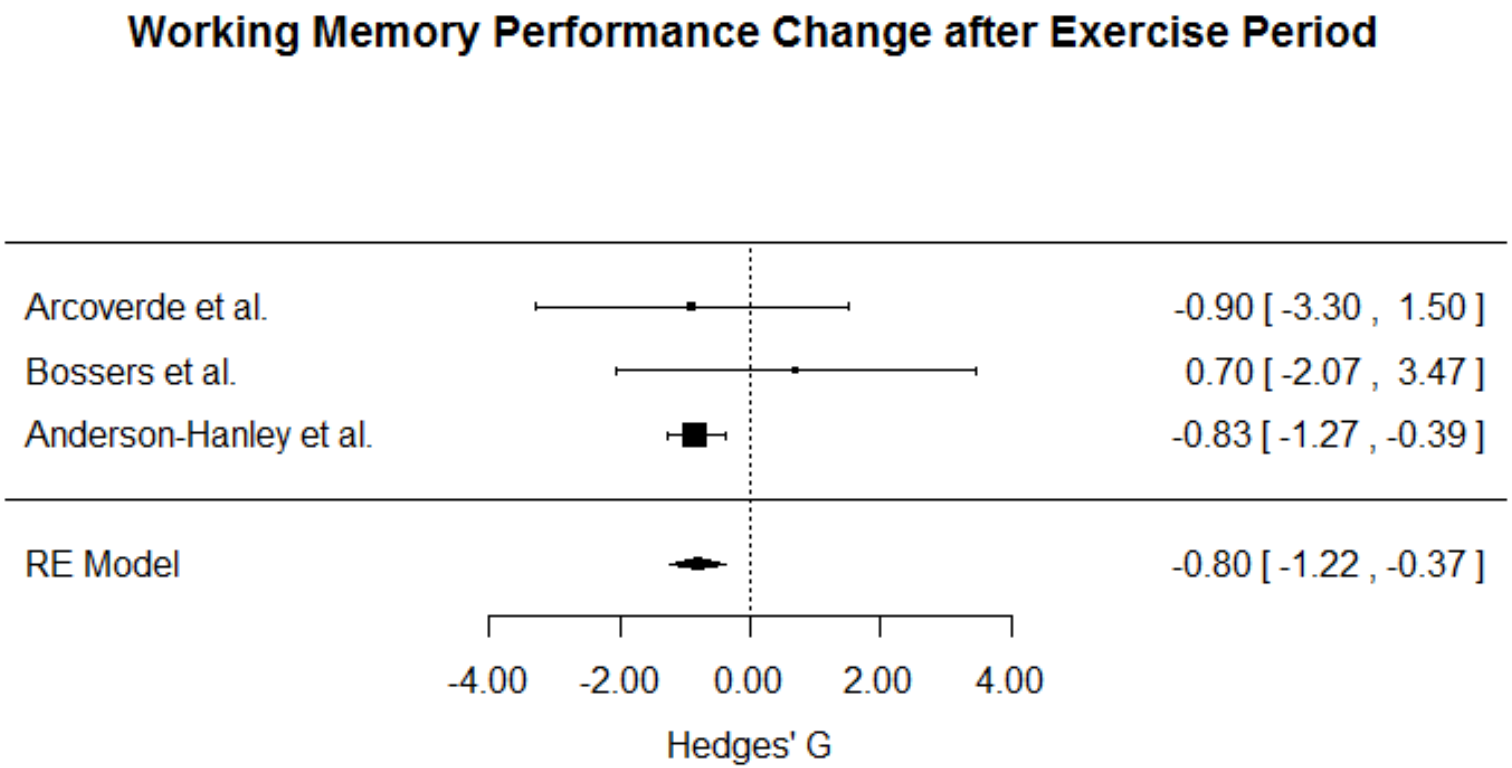

Figure 2: Working Memory Results

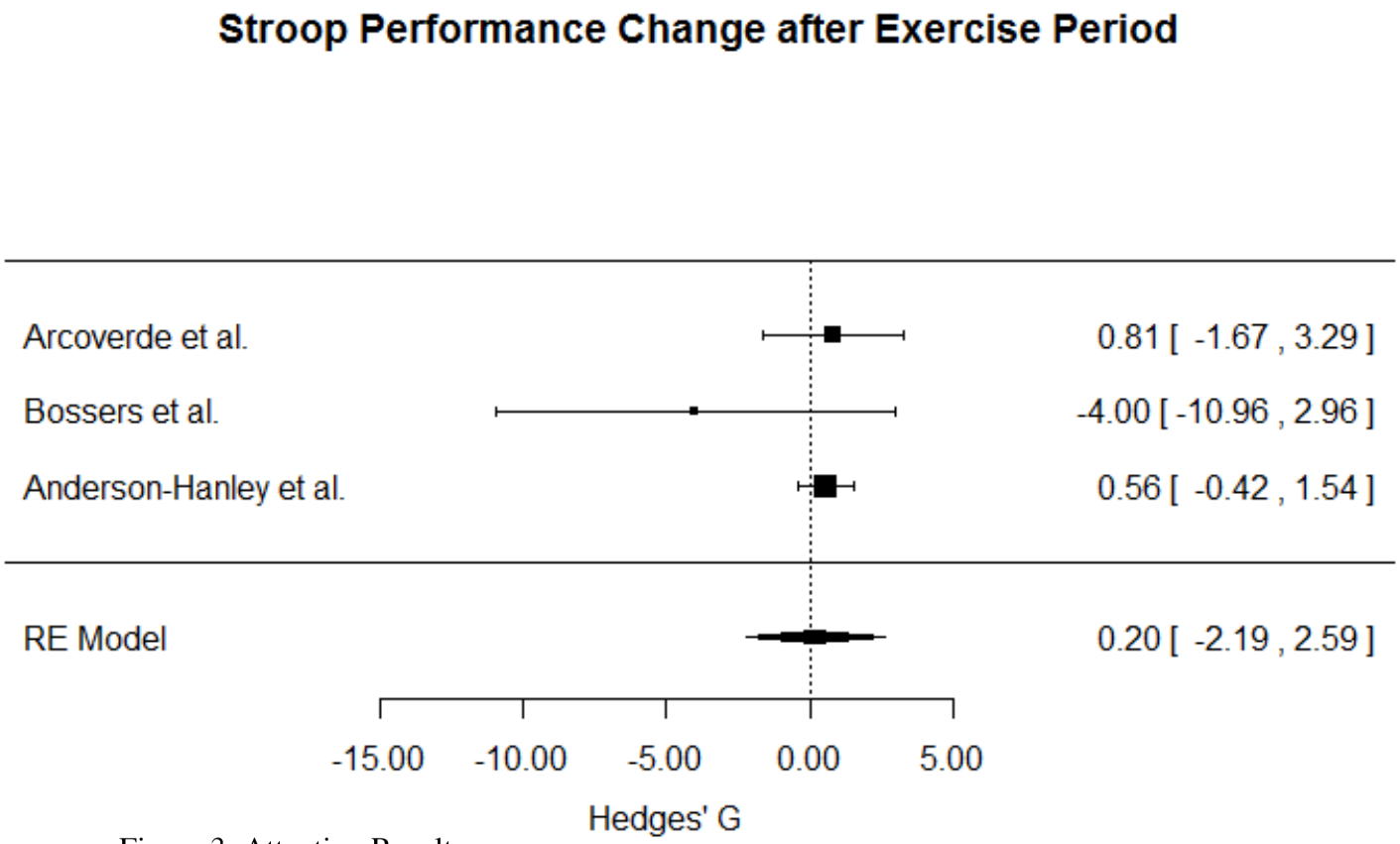

Figure 3: Attention Results

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
1	The Study of Mental and Resistance Training (SMART) Study-Resistance Training and/or Cognitive Training in Mild Cognitive Impairment: A Randomized, Double-Blind, Double-Sham Controlled Trial.		X						
2	What are the Benefits of Exercise for Alzheimerå«s Disease? A Systematic Review of Past 10 Years.					X			
3	Metabolic syndrome is associated with poor memory and executive performance in elderly community residents: the PROOF study.		X						
4	Exercise Training and Recreational Activities to Promote Executive Functions in Chronic Stroke: A Proof-of-concept Study.		X						

Table 2: Explanation of Eliminated Articles:
This table shows the reasons why each article was not chosen for analysis. This is shown with an "X."
Studies without an "X" were included in the analysis. This table is shown on pages 16-33.

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
5	Sleep Breathing Disorders and Cognitive Function in the Elderly: An 8-Year Follow-up Study. The Proof-Synapse Cohort.		X						
6	Effects of aerobic exercise on cognition and hippocampal volume in Alzheimer's disease: study protocol of a randomized controlled trial (The FIT-AD trial).						X		
7	Efficacy of antibody-based therapies to treat Alzheimer's disease: just a matter of timing?			X					
8	Maintaining health and wellness in the face of dementia: an exploratory analysis of individuals attending a rural and remote memory clinic.					X			

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
9	Associations between cognitive and gait performance during single- and dual-task walking in people with Parkinson disease.		X						
10	Memory intervention: the value of a clinical holistic program for older adults with memory impairments.			X					
11	Treadmill training as an augmentation treatment for Alzheimer's disease: a pilot randomized controlled study.								
12	Mitochondrial biogenesis: pharmacological approaches.					X			

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
13	Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: a systematic review.					X			
14	Alzheimer's disease and vascular dementia: one potentially preventable and modifiable disease? Part II: Management, prevention and future perspective.					X			
15	Feasibility of a combined aerobic and strength training program and its effects on cognitive and physical function in institutionalized dementia patients. A pilot study.								
16	The role of mobility as a protective factor of cognitive functioning in aging adults: a review.					X			

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
17	Central artery stiffness, neuropsychological function, and cerebral perfusion in sedentary and endurance-trained middle-aged adults.		X						
18	Apolipoprotein E gene, environmental risk factors, and their interactions in dementia among seniors.				X				
19	Treatment for mild cognitive impairment: systematic review.					X			
20	An economic evaluation of resistance training and aerobic training versus balance and toning exercises in older adults with mild cognitive impairment.		X						
21	Characterization of cognitive and motor performance during dual-tasking in healthy older adults and patients with Parkinson's disease.		X						

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
22	Cognitive dysfunction: an emerging concept of a new diabetic complication in the elderly.		X						
23	A community-based approach to trials of aerobic exercise in aging and Alzheimer's disease.						X		
24	History and experience: the direction of Alzheimer's disease.					X			
25	[Serum level of S100B as a marker of progression of vascular mild cognitive impairment into subcortical vascular dementia and therapy effectiveness].		X						
26	Slower gait, slower information processing and smaller prefrontal area in older adults.		X						

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
27	Recommended measures for the assessment of cognitive and physical performance in older patients with dementia: a systematic review.					X			
28	Walking while talking: investigation of alternate forms.		X						
29	Can healthy lifestyle modify risk factors for dementia? Findings from a pilot community-based survey in Chennai (India) and Newcastle (UK).					X			
30	Environmental enrichment has antidepressant-like action without improving learning and memory deficits in olfactory bulbectomized rats.	X							
31	Mild cognitive impairment and dementia: the importance of modifiable risk factors.					X			

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
32	[Cognitive impairment and the risk of falling in the elderly].					X			
33	Exercise training increases mitochondrial biogenesis in the brain.					X			
34	What makes a prognostic biomarker in CNS diseases: strategies for targeted biomarker discovery? Part 2: chronic progressive and relapsing disease.					X			
35	Memantine attenuates the impairment of spatial learning and memory of pentylenetetrazol-kindled rats.	X							

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
36	Evidence-based risk assessment and recommendations for physical activity clearance: cognitive and psychological conditions.					X			
37	Aerobic exercise to improve cognitive function in adults with neurological disorders: a systematic review.					X			
38	Dementia and legal competency.					X			
39	A randomized controlled trial of an activity specific exercise program for individuals with Alzheimer disease in long-term care settings.				X				
40	The effects on cognitive functions of a movement-based intervention in patients with Alzheimer's type dementia: a pilot study.								X

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
41	Gait stability and variability measures show effects of impaired cognition and dual tasking in frail people.			X					
42	The role of high-density lipoproteins in reducing the risk of vascular diseases, neurogenerative disorders, and cancer.					X			
43	Verbal fluency in Alzheimer's disease, Parkinson's disease, and major depression.			X					
44	Predictors of short- and long-term adherence to a daily walking program in persons with Alzheimer's disease.				X				

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
45	Dual-task performances can be improved in patients with dementia: a randomized controlled trial.			X					
46	The treatment of cognitive impairment associated with Parkinson's disease.		X						
47	How does dementia affect driving in older patients?					X			
48	The PACE study: a randomised clinical trial of cognitive activity (CA) for older adults with mild cognitive impairment (MCI).			X					
49	Quantitative gait analysis under dual-task in older people with mild cognitive impairment: a reliability study.			X					

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
50	[Systematized physical activity and cognitive performance in elderly with Alzheimer's dementia: a systematic review].					X			
51	Fatigue in Parkinson's disease patients.		X						
52	Vascular care in patients with Alzheimer's disease with cerebrovascular lesions-a randomized clinical trial.			X					
53	Does auditory rhythmical cueing improve gait in people with Parkinson's disease and cognitive impairment? A feasibility study.		X						
54	Psychosocial treatments of psychological symptoms in dementia: a systematic review of reports meeting quality standards.					X			

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
55	Pharmacotherapy guidelines for the aged by family doctors for the use of family doctors: part C--Special pharmacology.		X						
56	Health benefits of physical activity in older patients: a review.					X			
57	Sarcopenia in nursing home residents.				X				
58	Perceptions of Illness, coping, and well-being in persons with mild cognitive impairment and their care partners.		X						
59	Crash characteristics of older pedestrian fatalities: dementia pathology may be related to 'at risk' traffic situations.			X					

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
60	Wandering behaviour of persons with dementia in Korea: investigation of related factors.			X					
61	Exercise training for depressed older adults with Alzheimer's disease.				X				
62	Variability in the diagnosis and management of patients with Alzheimer's disease and cerebrovascular disease: results from the GALATEA multicentre, observational study.		X						
63	Impact of impaired executive function on gait stability.			X					
64	Risk of mortality following hip fracture in Japan.		X						
65	Walking while talking: effect of task prioritization in the elderly.		X						

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
66	The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer's disease.					X			
67	Aimless excursions: wandering in the elderly.			X					
68	The effect of rhythmic auditory stimulation (RAS) on gait characteristics of cadence, velocity, and stride length in persons with late stage dementia.			X					
69	Falls in elderly.				X				
70	Construction of a speed feedback therapy system to improve cognitive impairment in elderly people with dementia: a preliminary report.								X

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
71	[Role of psychiatry in prevention of accidental falling in the aged].				X				
72	Depression in the elderly: new concepts and therapeutic approaches.				X				
73	Cognitive and behavioural effects of music-based exercises in patients with dementia.				X				
74	Validation of the Algase Wandering Scale (Version 2) in a cross cultural sample.			X					
75	Alcohol, nutrition and health maintenance: selected aspects.					X			
76	Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease.			X					

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
77	Comparison of U.S., Canadian, and Australian participants' performance on the Algase Wandering Scale-Version 2 (AWS-V2).			X					
78	An exercise program for women who are caring for relatives with dementia.		X						
79	Effects of moderate-intensity exercise on physiological, behavioral, and emotional responses to family caregiving: a randomized controlled trial.		X						
80	[Clinically useful event-related potentials].			X					
81	Physical activity and risk of cognitive impairment and dementia in elderly persons.							X	
82	Dementia in Ayurveda.					X			

Number	Title	Non Human Study:	AD:	Exercise	Attention/ WM Testing:	Review Article:	No Results:	Long-term epidemiological study	No Stroop Test/ DSBW:
83	[Longitudinal and comprehensive follow-up study of the oldest man in Japan].					X			
84	The effects of additional pathology on the cognitive deficit in Alzheimer disease.			X					
85	[Sociomedical study of centenarians in Nagoya City].			X					
86	Predictors of skilled nursing placement in a multilevel long-term-care facility.			X					
87	[Geriatric medicine in future].					X			